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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/614,947	07/12/00	BRIERLEY R	02655-046005

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EXAMINER	
SAOUD, C	
ART UNIT	PAPER NUMBER
1647	5

DATE MAILED: 09/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/614,947	BRIERLEY et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 1-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites language of "a substantial amount" in step (b), "a significant proportion" in steps (f) , (i), (l) and (m), "a substantial proportion" in step (l). The skilled artisan is not able to determine the metes and bounds of the claims because these phrases are vague and indefinite. There is no support or guidance in the specification to allow the skilled artisan to determine what would constitute "a substantial amount", "a significant proportion", or "a substantial proportion", and therefore the claim is indefinite. Claims 2-21 are rejected because they depend on claim 1, and therefore are also indefinite.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention

was made, owned by the same person or subject to an obligation of assignment to the same person.

3. Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Holtz et al. (U.S. Pat. No. 5,231,178) in view of Hart et al. (Biotechnol. Appl. Biochem. 20: 217-232, 1994), Chang et al. (U.S. Pat. No. 5,288,931), Sofer et al. (Biotech. November/December: 198-203, 1983), and Skriver et al. (U.S. Pat. No. 5,459,052).

The disclosure of Holtz et al. is described in the instant application but will be summarized here for the sake of completeness of prosecution. Holtz et al. disclose a method of purification for IGF-I which includes all the steps of claim 1 except step (d) which is the refolding of IGF-I in buffer and step (k) which is the reverse phase chromatography elution (see Figure 1 of the instant specification and claims of Holtz et al.). Holtz et al. recites the limitations for claim 8 at col. 6, lines 10-21, claim 9 at col. 6, lines 22-35, claim 10 at col.6, lines 36-52, claim 13 at col. 6, lines 62-69 and col. 7, lines 1-5, claim 14 at col. 7, lines 6-22, claim 15 at col. 7, lines 36-51, claim 16 at col. 7, lines 52-66, claim 17 at col. 7, lines 67-68 and col. 8, lines 1-4, and claim 18 at col. 8, lines 5-15. Holtz et al. applies this purification method to IGF-I wherein the IGF is produced in transformed yeast. This IGF could be human and is necessarily recombinant. The promoter and transcription elements are specific for P. pastoris indicating a preference for this host (col. 5, lines 53-69 and col. 6, lines 1-9), thereby meeting the limitations of claims 2-7. Holtz et al. does not meet the limitations for claims 19-21 or 11-12 because unfolding/refolding buffer and reverse phase HPLC isolation of IGF-I are not disclosed.

Chang et al. teach a method for refolding misfolded IGF-I, including an unfolding/refolding buffer with a pH between 7.5 and 10.5. Misfolded IGF-I has significantly reduced biological activity and therefore, correct biologically active conformation are essential for processing functional proteins (col. 1, lines 54-69 and col. 2, lines 1-2). Various buffers are suitable to obtain this pH range and include CAPSO, AMP, CAPS, CHES, TRIS, and sodium acetate (col. 10, lines 8-17). The buffer also contains "the minimum amount of chaotropic agent and reducing agent necessary substantially to solubilize the IGF-I and allow refolding" (col. 9, lines 52-60). Examples of suitable reducing agents are DTT, BME, and cysteine. The preferred reducing agent is DTT at about 2-4 μM, BME at about 1-2 μM, or cysteine at about 2-4 μM (col. 10, lines 28-30). Applicants acknowledge in the instant Specification that borate is also a suitable buffering agent (as is TRIS). Hart et al. teach optimal conditions for IGF-I protein refolding including a refolding buffer with 2M urea, 1M NaCl, and 20% ethanol (see abstract). These references together teach the buffer conditions of claims 11 and 12, but do not teach the IGF-I purification method of the instant Application.

Skriver et al. teach a method for the purification of IGF-I which utilizes reverse-phase high pressure liquid chromatography (see Example 9, col. 13-14). Sofer et al. teach optimal chromatographic purification schemes for proteins. Specifically suggested are high-resolving techniques, including HPLC, for increased resolution as well as reduced separation time. The use of HPLC provide a means of separating proteins which differ by a single charge or by a difference in conformation, which increases the accuracy of isolating a specific protein (see page 200, lines 1-15). HPLC also reduces the time required for determining purity of the protein (page 202, col.

3, last paragraph). Skriver et al. and Sofer et al. do not teach the purification method of the instant Application.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Holtz et al. with the addition of a unfolding/refolding step (corresponding to step d of the instant claim 1) wherein the IGF is correctly folded by incubation in refolding buffer, as described by Chang et al. and Hart et al. One of ordinary skill in the art would have been motivated to include this step because Chang et al. teach the importance of correctly folded IGF-I for biological activity. It would have been obvious to include this step after the first elution because Holtz et al. indicate that the second eluting step would involve correctly folded IGF-I (see claim 1, step d). One of ordinary skill in the art would expect to obtain a greater yield of correctly folded IGF-I from the method of Holtz et al. because the refolding step recovers the IGF-I that is misfolded after the first elution step as well as expect a reasonable degree of success based on the teachings of the prior art.

It would also have been obvious to a person of ordinary skill in the art at the time the invention was made to replace the final gel filtration step of Holtz et al. with the reverse-phase HPLC step of Skriver et al. because both are filtration steps. One would be motivated to use a reverse-phase HPLC filtration step instead of the standard gel filtration step (claim 1, steps k-m) because Skriver et al. demonstrate the compatibility of IGF-I with the filtration system and Sofer et al. teach the advantages of using HPLC as a final isolating step in protein purification. The column matrix and buffer system is well known in the art and would only require routine optimization to obtain the limitations that are recited in instant claims 19-21. The skilled artisan

would expect to obtain the advantages of more accurate recovery of correctly folded IGF-I because HPLC permits the discrimination between molecules which differ by only a difference in conformation. Sofer et al. also teach that HPLC can reduce the time needed for isolation of the desired protein. Because the isolation of correctly folded IGF-I is important for biological activity, one of ordinary skill in the art would be motivated to include the HPLC filtration step in place of the gel filtration because it would increase the predictability of isolating IGF-I in a conformation that provides the maximum biological activity of the molecule.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art because the isolation of correctly folded IGF-I is desired in order to obtain a molecule with full biological activity, recombinant production of IGF-I can result in misfolded IGF-I, the method of Holtz et al. provides a process for isolation of IGF-I, and the teachings of Hart et al., Chang et al., Sofer et al., and Skriver et al. provide motivation and means for improving Holtz's method to allow for the isolation of correctly folded IGF-I.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-21 are rejected under the judicially created doctrine of double patenting over claims 1-21 of U. S. Patent No. 5,650,496 and 1-25 of U.S. Patent No. 6,207,806 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in '496 and '806 and is covered by the patents since the patents and the application are claiming common subject matter, as follows: methods of isolating correctly folded IGF-I. The instant claims do not include the dilute, weak acid and single ionic salt of claim 1 in '496, step (b) of the patent, but the instant claims encompass this subject matter because of the language of "comprising". The instant claims appear to be essentially the same as the claims of '806, and encompass the same subject matter because of the language of "comprising".

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

6. In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents **must** be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556. If this number is out of service, please call the Group receptionist for an alternate number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

September 17, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud